

REMARKS/ARGUMENTS

1. Rejections Under 35 USC 102(b)

The Examiner rejects claim 10 under 35 USC 102(b) as being anticipated by U.S. Patent No. 5,162,336 to Molino, et al.

The Examiner also rejects claim 10 under 35 USC 102(b) as being anticipated by Nemes, et al., "A Convenient Synthesis of Conformationally Constrained B-Substituted Tryptophans."

The Examiner also rejects claim 16 under 35 USC 102(b) as being anticipated by U.S. Patent No. 5,985,834 to Engel, et al.

The Examiner also rejects claim 17 under 35 USC 102(b) as being anticipated by Wei-Min, et al., "Chiral Ligands Derived From Abrinbe.3. Asymmetric Pictet-Spengler Reaction of Abrine Methyl Ester and Synthesis of Chiral 1,2,3,4-Tetrahydro-B-carbolines as Promoters in Addition of Diethylzinc toward Aromatic Aldehydes."

The Examiner also rejects claims 20 and 21 under 35 USC 102(b) as being anticipated by Yang, et al., "Facile Cleavage of the Carbamate Linker of Hydroxymethyl Resin and its Application in Synthesis requiring Strongly Acidic Conditions."

The Examiner also rejects claims 22 and 23 under 35 USC 102(b) as being anticipated by Yang and Guo, "Pictet-Spengler Reaction on Solid Support."

The Examiner rejects claims 24 and 25 under 35 USC 102(b) as being anticipated by EP Patent No. 0466548 to Levy, et al.

The Examiner also rejects claims 27 and 28 under 35 USC 102(b) as being anticipated by Dondas, et al., "Sequential 1,3-Dipolar Cycloaddition-Pictet-Spengler Reactions. A Versatile Tactical Combination."

Applicants amend independent claim 10 to specify particular M groups. Support for this amendment appears in the Specification at paragraph 115 and also in original claim 37. None of the references relied upon by the Examiner in support of the various rejections under 35 USC 102(b) teach the particular M groups now specified in independent claim 10. Accordingly, none

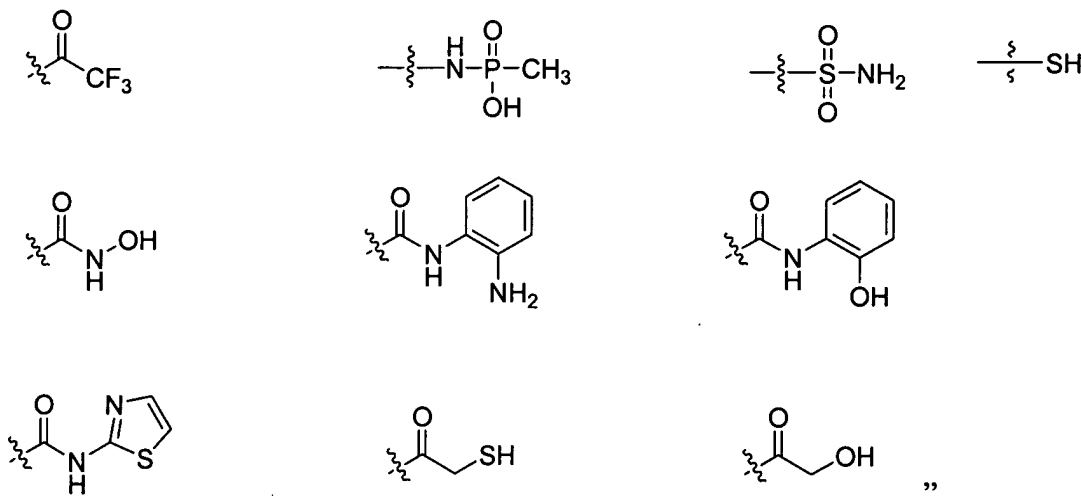
of the pending rejections for anticipation under 35 USC 102(b) should be maintained in view of the current amendment to independent claim 10. Furthermore, none of the references relied upon by the Examiner teach or suggest that the compounds disclosed therein have any activity against histone deacetylase. Withdrawal of each of the pending art rejections is therefore respectfully requested.

2. Rejection Under 35 USC 112, First Paragraph

The Examiner rejects claims 10 and 16-38 under 35 USC 112, First Paragraph on the grounds that the rejected claims fail to meet the written description requirement. Specifically, the Examiner states that that “the Specification defines the M and L moieties with general moieties and examples, which does not clearly and unambiguously define the structure of the compounds.”

a) M

In regard to M, Applicants amend independent claim 10 to specify that “M is selected from the group consisting of:



Applicants submit that this amendment to independent claim 10 should overcome the Examiner's rejection under 35 USC 112, First Paragraph. Applicants also take this opportunity to add dependent claims 39-48 which claim each of these M substituents independently.

b) L

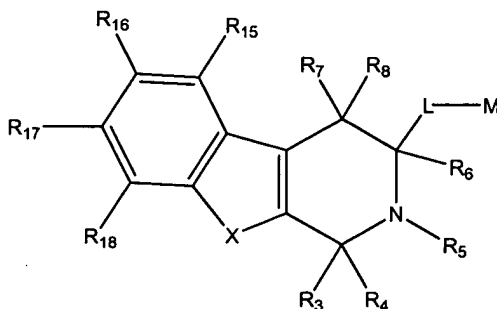
Applicants traverse the Examiner rejection under 35 USC 112, First Paragraph with regard to L and submit that “a substituent comprising a chain of 3-12 atoms connecting the M substituent to the carbon atom alpha to the L substituent” defines a scope for L based on the structure of L that satisfies 35 USC 112, First Paragraph.

The Examiner’s attention is drawn to the following sentences from paragraph 117 of the Specification where the purpose behind the specified structure for L is explained:

the number of atoms in the chain serves to extend the zinc complexing substituent, M, a sufficient distance away from the remainder of the inhibitor so as to allow the zinc complexing substituent to interact with the zinc ion while the remainder of the inhibitor interacts with hydrophobic regions in the binding pocket of the histone deacetylase.

Based on this teaching, one of ordinary skill would fully understand that the key structural feature of L is to provide 3-12 atom separation between the M substituent to the carbon atom alpha to the L substituent. This is precisely what is being claimed in independent claim 10.

The clarity of the definition for L provided in the claims is illustrated in regard to the compound that Applicants specifically elected in their Response to Restriction Requirement, reproduced below:

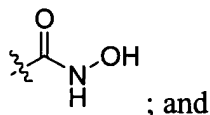


wherein

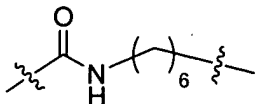
R₃, R₄, R₅, R₆, R₇, R₈, R₁₅, R₁₆, R₁₇ and R₁₈ are each hydrogen;

X is NR_{14} , where R_{14} is hydrogen;

M is



L is



One of ordinary skill in the art can readily see that this particular embodiment of L possesses a chain of 8 atoms separating M from the ring carbon (i.e., the carbonyl carbon, the amide nitrogen, and the six carbon atoms forming $-(\text{CH}_2)_6-$).

The teachings provided in the Specification also make it clear that the definition provided for L is intended to be open ended so as to allow for a wide range of substituents on the 3-12 atom chain that provides the desired separation between the M substituent to the carbon atom alpha to the L substituent. For example, paragraphs 121 – 134 of the Specification provide extensive teaching to one of ordinary skill in the art with regard to the wide range of substituents that may be used to possess the structural feature of a chain of 3-12 atoms connecting the M substituent to the carbon atom alpha to the L substituent. In view of this teaching, one of ordinary skill would fully comprehend that L is intended to encompass any substituent which when positioned between M and the ring system provides 3-12 atom separating the M substituent from the ring atom shown in claim 10 to which L is attached. Applicants presently amend claim 10 in order make it clear that the specified chain of 3-12 atoms may be substituted or unsubstituted.

In support of the Examiner's rejection, the Examiner states that exemplification is not an explicit definition. However, as explained above, Applicants believe that they have provided both an explicit and clear definition (See paragraph 117) as well as robust exemplifications (See paragraphs 121-132) to assist one of ordinary skill to fully comprehend the intended scope of L, as defined. The Examiner is therefore respectfully requested to withdraw the pending rejection

of the claims under 35 USC 112, First Paragraph with regard to the use of L in independent claim 10.

10. Rejection Under 35 USC 112, Second Paragraph

The Examiner rejects claims 10 and 16-38 under 35 USC 112, Second Paragraph on the grounds that the rejected claims are indefinite.

a) Definition of L and M

The Examiner objects to claims 18-36 on the grounds that L and M are not properly defined. The Examiner objects to claim 37 on the grounds that L is not properly defined and objects to claim 38 on the grounds that M is not properly defined.

i) M

As described above, Applicants amend independent claim 10 to recite that M is selected from a specific group of structurally defined substituents. Applicants submit that the Examiner's objection with regard to the definiteness of M is overcome by the present amendment to claim 10 with regard to M.

i) L

Applicants traverse the Examiner's objection with regard to L and submit, as discussed further with regard to the Examiner's rejection under 35 USC 112, First Paragraph, that L is definite such that one of ordinary skill in the art would understand the metes and bounds of L. Specifically, Applicants fail to see how one of ordinary skill would not be able to count the number of atoms positioned between M and the carbon ring atom to which L is attached and determine whether there are between 3-12 atoms separating M from the ring atom. Withdrawal of the objection to L under 35 USC 112, Second Paragraph is therefore respectfully requested.

b) Claim 18

The Examiner also objects that claim 18 does not have sufficient antecedent basis in claim 10 because claim 18 expands the breadth of claim 17 and claim 10 with regard to R^3 .

Applicants amend claim 17 to specify that “the moiety attached to the ring carbon is a substituted or unsubstituted branched C_1 - C_{10} alkyl, aminoalkyl, or oxaalkyl.” Claim 18 further narrows claim 17 by specifying particular substituents for the branched C_1 - C_{10} alkyl, aminoalkyl, or oxaalkyl. The Examiner is respectfully requested to withdraw the pending objection to claim 18 in view of the present amendment to claim 17.

c) Claim 19

The Examiner also objects to claim 19 on the grounds that claim 10 does not define R^3 to further comprise the limitations recited in claim 19.

Applicants amend claim 17 to specify that “the moiety attached to the ring carbon is a substituted or unsubstituted branched C_1 - C_{10} alkyl, aminoalkyl, or oxaalkyl.” Claim 19 further narrows claim 17 by specifying particular substituents for the branched C_1 - C_{10} alkyl, aminoalkyl, or oxaalkyl. The Examiner is respectfully requested to withdraw the pending objection to claim 19 in view of the present amendment to claim 17.

d) Claim 28

The Examiner also objects to claim 28 on the grounds that claim 10 does not provide antecedent basis for R^5 and R^6 to come together to form a ring, as specified in claim 28.

Applicants amend claim 10 to specify that R_5 and R_6 may be “taken together to form a 3, 4, 5, 6, 7 or 8 membered ring.” The Examiner is respectfully requested to withdraw the pending objection to claim 28 in view of the present amendment to claim 10.

e) Claims 29 and 30

The Examiner also objects to claims 29 and 30 on the grounds that claim 10 does not provide antecedent basis for R^6 and R^7 to come together to form a ring, as specified in claim 29.

Applicants amend claim 10 to specify that R_6 and R_7 may be “taken together to form a 3, 4, 5, 6, 7 or 8 membered ring.” The Examiner is respectfully requested to withdraw the pending objection to claims 29 and 30 in view of the present amendment to claim 10.

f) Claim 33

The Examiner also objects to claim 33 on the grounds that claim 10 does not provide antecedent basis for an imine being further substituted.

Applicants traverse the Examiner’s objection with regard to claim 33. Applicants purposefully specified in claim 10 that R_7 and R_8 are each independently selected from a group of substituents comprising a moiety attached to the ring carbon selected from the group consisting of.” “Comprising” was used as an open ended term to not preclude that the moiety may optionally be further substituted. To make this intention clearer, Applicants add “in each case unsubstituted or further substituted through available valencies” in order to indicate that all of the members of the markush group may be substituted or unsubstituted, including the imine. This intention is further supported by the Specification which teaches at paragraph 82 that “it is noted in regard to all of the definitions provided herein that the definitions should be interpreted as being open ended in the sense that further substituents beyond those specified may be included.” Withdrawal of this ground of rejection is respectfully requested.

g) Claim 34

The Examiner also objects to claim 34 on the grounds that the alkene specified in claim 34 is chemically unstable. Applicants note that one of ordinary skill in the art would know how to select combinations of R_{10} and R_{11} where the resulting alkene would be stable. Applicants

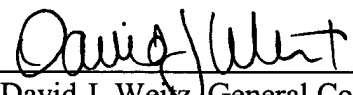
nonetheless reviewed the scope of claim 34 and eliminated certain substituents that may result in less stable compounds. Withdrawal of this ground of rejection is respectfully requested in view of the amendment to claim 34.

CONCLUSION

Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,
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